SILICOSIS AND MINERS' PHTHISIS.

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IT has long been recognised that certain occupations predispose to pulmonary tuberculosis, and that in these "dangerous" occupations the death-rate from this disease is far higher than in the general population. This is particularly so among those who work habitually in atmospheres which are laden with silica dust. The silicotic lung itself is a well-recognised pathological entity, presenting, in addition to the general increase in bulk of the connective-tissue trabeculæ common to all forms of pneumoconiosis, the development of nodules or groups of nodules of dense fibrous tissue which often surround visible particles of silica. This condition, in itself sufficiently serious, is, however, of immeasurably greater importance from the fact that the silicotic lung is far more vulnerable to invasion by bacteria, and especially by the tubercle bacillus, than the normal organ. The general facts which have been accumulated, and upon which these conclusions are based, have been summarised by Collis in the Milroy Lectures for 1915. The association of tuberculosis with silicosis in Cornwall has been established by Haldane (1904); in South Africa by Watkins Pitchford (1916) and his collaborators. Experimentally, Gardner (1920) has been able to show that a dust containing a large percentage of silica influences profoundly the course of a tuberculous infection of the lungs of guinea-pigs. Gardner used a strain of tubercle bacillus of such low virulence that "guinea-pigs infected by inhalation of this strain show lung tuberculosis, which, however, clears up with restoration of function." When guinea-pigs were dusted with a granite dust and infected with tubercle, the lungs, instead of showing "a compact, sharply circumscribed tubercle," show "a central solid mass with heavy radiating peripheral processes." There is an early and progressive fibrosis in the dusted animals which tends to retard the healing of the tuberculous lesions.

Thus, clinically, there is overwhelming evidence that silica induces a fibrosis of the lungs, which are then sensitive to tuberculosis; and experimentally there is sound evidence supporting the clinical conclusions. The explanation of these facts is yet to be sought. The greater part of the experimental work which has been done on the subject has been concerned with the mode of entry of the dust into the lungs; the literature on this is very large, and the reader is referred to Collis' lectures and to Willis (1921) for the bibliography. It may now be said that there is general agreement that the very fine particles of dust which reach the lung alveoli are taken up by phagocytes, which, according to most authors, are derived from the endothelium of the lung capillaries, and, according to others, from alveolar epithelium, and that the dust-laden phagocytes migrate to the nearest lymphoid tissue and gain access to the closed lymphatic vascular system which drains

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the lung. Most dusts are removed from the lung in this way through the lymphatic channels, but silica, for the most part, remains *in sitû*, stimulating the formation of new connective tissue.

The two problems arising out of the recorded knowledge which have occupied our attention during the last two years are:

(1) Why is silica, conspicuous and possibly alone among common dusts, capable of inducing extensive fibrosis?

(2) How does the silicotic fibrosis aid the establishment of tuberculosis?

(1) There have been many attempts made to answer the first question. For the most part, however, the answers have not been based upon experimental study. The view most often expressed is that silica owes its injurious quality to its physical properties (Watkins Pitchford, Oliver, Moore and others). Moore (1918) tabulates the properties as follows: "(1) Its heaviness; (2) its sharp vitreous fracture; (3) its great hardness and insolubility." Hardness, heaviness and sharpness of points or edges are properties which lose their significance when applied to particles of dust enclosed in the cytoplasm of wandering cells; direct mechanical injury to the lung (in the circumstances under which dust gains access) is almost inconceivable. The property of insolubility deserves more attention. Silica (SiO_2), though insoluble in all acids except hydrofluoric, is readily dissolved in alkalis. By boiling finely divided silica in a solution of Na_2CO_3 sodium silicate is formed. The statement, therefore, that silica dust is insoluble is only partially true, and the conditions under which a solution may be obtained are relevant to the problem of silicosis. Carbon particles—certainly in the test-tube—are more insoluble than silica particles, and it is universally agreed that carbon dust, unless in large amounts, is of no pathological importance. The suggestion, therefore, that an inhaled dust may, *in virtue of its insolubility*, exert a harmful action on the tissue is contrary to observed facts. Moreover, it is contrary to modern conceptions of the energetics of the body. In silicosis the injury to the lungs is a continuous process, and the amount of fibrous tissue formed is much greater than can be explained upon any mechanical process involving disturbance of microscopic anatomical relationships. Further, the fibrosis extends far beyond the near neighbourhood of the silica particles. In order that a continuous reaction between cells and a dust should ensue, molecular or submolecular contact must be established. Just as, in a physiological sense, no material is of use for energy purposes unless it is soluble, so, pathologically, with certain obvious mechanical exceptions, it is only soluble substances which can exert a substantial or a continuous effect on the tissues.

Haldane (1918) offers another answer to the question, "Why is pure quartz so difficult to remove from the lungs?" He supposes that coal-dust, shale, etc., owe their properties to a high adsorptive power, of which silica possesses little or none. Thus dust particles are attractive to dust-cells in proportion to the soluble substances adsorbed. The explanation is, therefore, that silica, adsorbing little or none of the substances which stimulate phagocytosis, is not removed from the lungs. But as we know that the way by which silica is carried into the lymphatics of the lungs is by the dust-cells this answer appears to us to be unsatisfactory.

Mellor (1918), in a written contribution to the discussion on Haldane's paper, draws attention to the surface of the small particles of silica. He states that "the surface of the fine grains of silica was sometimes found to be corroded, so that the surface appeared to be covered with a film crust of colloidal silica." It has been shown that colloidal silica is a toxic substance (Gye and Purdy, 1922), and Mellor's observation may, therefore, provide an answer to the problem which is the reverse of Haldane's, namely, that the film of colloidal silica on the particles, whilst not preventing phagocytosis, does diminish the mobility of the phagocytes, which are slowly poisoned. Mavrogordato (1922) shows that the dust-cells are immobilised in the lymphatic channels, and suggests that they become fixed and preserved by the action of the silica which they carry. Collis includes in the list of properties of silica dust, which may be significant in the solution of the problem of silicosis, the chemical property of "acidity, which, owing to the presence of the element silicon, may render the particles capable of entering into and modifying the colloidal structure of protoplasm." The meaning of this is not clear. The trend of opinion, therefore, is in favour of the view that silica causes fibrosis by acting chemically upon the tissues, and not in virtue of its physical properties.

(2) The second problem is even more difficult, and much less work has been done on it. The disorganisation of the lymphatic system in silicosis has been recognised by most authors as a potent factor in the increased susceptibility to tuberculosis. Gardner accepts this view, but adds a further explanation of the prevalence of tuberculosis among the victims of silicosis. He regards silica dust and the tubercle bacillus as irritants, and the two "acting together are capable, in a short time, of setting in motion a series of reactions on the part of the lung which neither alone is capable of initiating. By concentration of both in small foci each reinforces the action of the other, resulting in a chronic lesion which is slow to heal." Our own work on this question is the outcome of investigations into the factors influencing infection and immunity which have occupied our attention for some time. Among other substances we have used silica as a means of breaking down the normal resistance of tissues to invasion by micro-organisms, and while working with *B. tuberculosis* we obtained results which seem to have a direct bearing upon the pathology of miners' phthisis, and suggested further inquiries along these lines. The principal element in the problem of miners' phthisis is that men who are resistant to tuberculosis become susceptible with the development of silicotic fibrosis. It is important to understand the mechanism of this increased susceptibility, not merely as a part of the problem of industrial tuberculosis, but also because general tuberculosis presents a similar though more subtle problem.

Our work has been based on the known facts—(1) that colloidal silica is a cell poison; (2) that colloidal silica is the most easily formed soluble form of silica, the circulation of silica in nature depending upon this; and (3) that living matter (soil bacteria) is able to break up mineral silicates with formation of soluble silica (Bassalik, 1913). We judged it probable that the fibrosis brought about by finely-divided silica was due to the *slow* formation in the tissues of silica sol, either directly or through the intermediate formation of sodium silicate which is decomposed by carbonic acid, the sol formed acting as a cell poison. The direct proof of this has been found impossible, and we are, therefore, compelled to fall back upon indirect evidence. The considerations which we think rule out the "physical" explanation of silicosis have already been given; the indirect evidence which supports our hypothesis is given below.

Experimental.—In approaching experimentally a subject of this complexity it is obviously necessary to proceed from the most simple experiments to those in which several factors are concerned, and we have attempted to clear the ground by studying the effects of pure silica (SiO_2), of a powder containing 40 per cent. water and of silica sol in the subcutaneous tissue. This has been followed by experiments in which tubercle bacilli have been injected in association with silica or with an inert substance (carbon). Mice were chosen as experimental animals in the earlier work, partly because of their convenience as to size, etc., but chiefly because they possess a high degree of resistance to tuberculosis, though the resistance appears to be rather different from that exhibited by man.

Our technical methods have differed from those adopted by most workers in this field. We have used subcutaneous inoculations rather than dust inhalations, because of the greater ease with which local reactions could be followed.

THE RESULTS OF INJECTING SILICA INTO THE SUBCUTANEOUS TISSUE.

In these experiments the soluble colloidal form of silica, orthosilicic acid $Si(OH)_4$ and the insoluble silica (SiO_2) were dissolved or suspended in normal neutral salt solution, and injected in doses of 2 mgrm. into the subcutaneous tissue of the flank. For the most part mice were used in these experiments, but from time to time results were compared with similar lesions produced in guinea-pigs and rabbits. The animals were killed at stated times, the local lesions carefully dissected out and fixed in Zenker's fluid or formol salt solution, and embedded in paraffin. Sometimes serial sections were prepared of the whole of the lesion, but more often it was found sufficient to examine groups of sections from different levels of the block.

It may be said at once that there is no essential difference between the reaction produced by soluble silica and that which follows the injection of the insoluble forms. The only obvious difference is that the reaction is more rapid and more transient with colloidal silica, and our findings support very strongly the view that SiO_2 becomes soluble by hydration in the tissue; but, inasmuch as with insoluble silica the reaction is somewhat delayed, the lesions produced by this substance lend themselves rather more readily to analysis than those produced by colloidal silica.

Within three hours after injection of SiO_2 a recognisable microscopic lesion is produced. It consists of an area of granular coagulation necrosis quite acellular except at the periphery, where a few of the fixed connective-tissue cells of the part can be recognised, and an occasional polynuclear leucocyte.

Five hours after the injection the lesion is more clearly defined. The centre of the focus is still quite acellular, consisting of a coagulum which has entirely replaced the fibrillar connective tissue; with different fixatives the coagulum appears granular to a greater or less degree, but these variations are entirely mechanical, and the essential process is a coagulation necrosis of the tissue itself, and the serum poured into it. The periphery of the lesion is now more clearly defined by a zone of leucocytes, and by the crowding together of the fixed connective-tissue cells. Beyond the lesion for some distance, even in the neighbouring inguinal lymphatic gland, the capillaries are dilated and filled with blood, and present an active margination and emigration of leucocytes. It may be noted that silica injected into the tissue in this way has no specific action on the endothelium of blood-vessels. Occasionally a venule may be seen containing a delicate coagulum, but for the most part there is no thrombosis. Only in the actual lesion do the venules undergo destruction in common with muscle-fibre, nerves, and the connective tissue.

An hour or two later shows an active invasion of the periphery of the focus by leucocytes, but many of these exhibit degeneration with pyknosis and karyorrhexis of their nuclei. Further, it is obvious that the lesion has not been delimited by the reaction of the tissue, for, especially in the silica lesion, there is a spreading necrosis beyond the marginal zone of leucocytes. In the silicic acid lesion this is not always so noticeable, the explanation being that the deleterious action of the soluble poison is manifested immediately, whereas the insoluble silica becomes soluble gradually, so that its action is potent over a longer period of time.

In seventeen hours the focus is extensive. It exhibits a central acellular zone, varying somewhat in extent, but the greater part of the necrotic area is densely infiltrated with leucocytes, though these themselves are often enough degenerated and fragmented. The coagulum appears to be denser and more inspissated, presumably by the loss of fluid, and it is broken up into spherical masses which are surrounded by leucocytes. The venules are still dilated and engorged.

In forty-two hours the lesion is noticeably more localised. The general characters are the same, but there appears to be some compression of the connective tissue at the periphery, with the formation of a delicate limiting wall. Possibly also actual proliferation of fibroblasts helps in the production of this barrier.

The later stages of the lesion are characterised by the gradual shrinkage of the coagulum, the appearance at the periphery of large mononuclear cells with irregular outlines and vacuolated protoplasm, and the active proliferation of connective tissue with the formation of numerous capillaries. The final stages are those of an organising inflammatory fibrosis, but the process lasts a considerable time, and the remains of the necrotic tissue persist for ten days at least.

These are the general features of the subcutaneous silica lesion as we have observed them. It may be modified in its extent and duration, but such variations as we have observed do not appear to be of fundamental importance. While it is comparatively easy, however, to study the earlier lesions, it is much more difficult in those which have been allowed to go on to three or more days. The macroscopic lesion is itself far from easy to define, and it often happens that the microscopic preparations leave something to be desired. In any series of experiments the later results have been difficult to observe, and this has necessitated much repetition of the work. It is possible, of course, to define the experimental area by some inert colouring matter such as carbon, but we wished to avoid complicating factors as far as possible, and have therefore relied upon composite pictures obtained from the most satisfactory stages in several experiments. There is, then, a very definite tissue reaction to silica; it is, in fact, so far as our experience of non-bacterial irritants goes, specific. The question therefore arose whether this reaction differed from others in aiding in some specific way the growth of the tubercle bacillus. A comparison between the results obtained by inoculating tubercle bacilli alone and in combination with silica gives interesting results.

INOCULATION OF TUBERCLE BACILLI ALONE.

The picture varies enormously according to whether a thick or a thin emulsion of bacilli is used.

With a thick emulsion there is a brisk reaction of the connective tissue, the vessels become dilated, and margination and emigration of leucocytes is obvious as soon as three hours after inoculation. The centre of the lesion consists of a small space in the areolar tissue containing tubercle bacilli. This is surrounded by a thin zone of leucocytes which are actively phagocytosing the bacilli, as are also the fixed connective-tissue cells of the part. Often the wandering phagocytes appear to be emigrating to the lymph-gland, but none can be distinguished within it.

In six hours after inoculation the centre of the lesion consists of an irregular space containing granular material with bacilli at the margin. Immediately around this there is a dense zone of leucocytes, many of them loaded with bacilli. Where clumps of bacilli appear, as often happens with thick emulsions, they are entirely surrounded by leucocytes. Outside this zone the connective tissue is highly cellular, the cells being leucocytes, fixed connective-tissue cells and mast-cells, and there are unusually large numbers of mast-cells around the margin of the lymph-node. Occasionally a stray phagocyte can be seen filled with bacilli, and obviously migrating towards the gland, but it is very rare to encounter such cells actually within the gland.

In nine hours there is a complete alteration in the picture. The general congestion and leucocytic infiltration has passed off, and the loose areolar tissues show little change from the normal. The lesion, however, has become definitely localised as an abscess consisting almost entirely of polynuclear leucocytes. The majority of these contain bacilli, and some are absolutely loaded with them. The general impression given is that of a much larger number of bacilli than in the earlier stages, though they are all intracellular. Around the abscess the connective-tissue fibrils are compressed to form a definite wall, though a delicate one. Outside this are leucocytes in moderate numbers—several packed with bacilli—and there appears to be slight proliferation of the fixed connective-tissue cells.

In twenty-four hours the abscess is even more clearly defined, and contains several small spherical spaces, empty except for bacilli, which are separate, not in clumps. There is intense phagocytosis. Outside the abscess there are a few isolated bacilli and cells which have phagocytosed bacilli, but there is little general change except for some connective-tissue cell proliferation around the wall.

The later stages of the inoculation with massive doses of tubercle bacilli were studied in preparations from several different experiments, and a fairly satisfactory composite picture of the progress of the lesion has been obtained. The whole process is remarkably quiescent. There is often an indolent proliferation of the fixed connective-tissue elements at the periphery, and the abscess becomes encapsulated with a broad zone of dense fibrous tissue, which is acellular, and appears to be formed partly by compression and partly by the gradual deposit of collagen fibres. Mononuclear cells wander into the abscess in considerable numbers, ranging themselves at the periphery; they are actively phagocytic. In the course of time they replace entirely the leucocytes, which undergo gradual necrosis and lysis, sometimes to such an extent that the centre of the abscess is occupied by a structureless coágulum. In the surrounding areolar tissue occasional polynuclear and mononuclear phagocytes containing many bacilli can be seen. These eventually reach the lymph-gland and deposit their bacilli, which cause a slow, indolent reaction of the endothelial and reticular cells, which form multiple minute microscopic foci in the gland. After a period of three months or more the local lesion consists simply of a group of extremely vacuolated mononuclear cells containing granular bacilli, surrounded by dense fibrous tissue. This nodule is surrounded by a zone of fibroblasts and polyblasts of varying density.

A rather clearer picture of the reaction is obtained by the study of lesions produced by injection of extremely fine emulsions. The following is the protocol of such an experiment:

24 *hours.*—The lesion consists of a very small focus, a cavity in the areolar tissue containing in one or two sections of the series a minute coagulum, around which is a small bunch of cells. Cells are scattered sparsely in the cavity; they are rather thicker at the margin, fading off into the peripheral tissue. There are a few mononuclear elements, fixed connective-tissue cells or polyblasts, but the majority of the cells are polynuclear leucocytes. There are very few bacilli—scarcely one in each section—and they are all phagocytosed.

2 *days.*—A small diffuse focus of cell infiltration consisting of wandering cells, fibroblasts and a few polymorphs. More bacilli can be seen than in the 24-hours lesion, all phagocytosed.

3 *days.*—A very small lesion consisting chiefly of macrophages with foamy cytoplasm; a few bacilli in the cells.

7 *days* (Fig. 2).—A slight indefinite lesion consisting of an accumulation of mononuclear cells, polyblasts and fixed connective-tissue elements. Small groups of bacilli can be seen from time to time lying free in the tissues or within the bodies of fibroblasts. They consist of some ten or more bacilli tightly packed together, and suggest proliferation of the organisms *in sitû*. The focus passes into a dilated lymph trunk at the side of the gland, and bacilli can be seen lying free in this with a few mononuclear cells.

The tubercle bacillus possesses only a very slight degree of pathogenicity for the mouse, and this applies equally to human and bovine strains. It can survive and proliferate in the tissues, but it causes very little reaction. When present in small numbers the local reserves of the tissue appear sufficient to cope with it, though when injected in massive doses it calls forth a pronounced exudation of polynuclear leucocytes. It is readily phagocytosed by the fixed connective-tissue cells or polyblasts as well as by wandering leucocytes, but it can exist for a long period in the bodies of such cells without any apparent change; in fact, it seems likely that it can actually proliferate within phagocytes. It seems to cause no cell necrosis or tissue destruction, and though it may be transported, chiefly by the agency of phagocytes, to lymphatic glands and the viscera, in these secondary foci it gives rise only to a very moderate degree of tissue reaction quite unlike that seen in susceptible animals. It would seem, therefore, that tuberculosis in the mouse ought to provide a particularly favourable opportunity for studying the influence of silica in the tuberculous process.

INOCULATION OF TUBERCLE BACILLI WITH SILICA.

We have observed repeatedly that an injection of tubercle bacilli accompanied by silica into the subcutaneous tissue gives rise to a much greater local reaction than an injection of tubercle bacilli alone, and further, that general dissemination is earlier and more active. The silica effect, however, is transient, so that we have, in these experiments, inoculated fresh doses of silica weekly into the local lesion, though the dose of tubercle bacilli has not been repeated. In this way we have produced large abscesses containing enormous numbers of tubercle bacilli, far more than were originally injected, but the common silica lesion produced in this way so complicates the microscopic picture that it is impossible to arrive at a clear conception of what takes place. We have, therefore, resorted to the "early stages" method of analysis. The changes are brought out well in an experiment in which silicic acid was inoculated together with a very fine emulsion of tubercle bacilli suspended in normal saline. In twenty-four hours a considerable lesion is produced, consisting of a central fine coagulum with an outer zone of leucocytes, the whole being bounded by a thin limiting coagulum. A very few bacilli can be seen in the central zone. There is general congestion and leucocytosis in the neighbouring areolar tissue.

In two days the lesion has progressed. The central coagulum is now rather denser and contains rather more bacilli. None of these are as yet phagocytosed. The peripheral leucocytosis is as obvious as in the 1-day preparation.

In three days the central coagulum contains more bacilli and there is now some early reaction in the peripheral connective tissue.

In five days the lesion is more advanced. The central coagulum is dense and contains many more bacilli than in the earlier foci. There is much necrosis of the leucocytes in the intermediate zone, and in the external necrotic zone, which is by now extensive, there is a considerable accumulation of large mononuclear cells with an irregular outline and a vacuolated cytoplasm, probably endothelial cells. There is much new capillary formation at the periphery of the lesion and in the inner part of the external necrotic zone.

The six days' lesion (Fig. 1) is a large one, resembling in general character the previous ones. At the periphery there is an intense fibroblastic and angioblastic reaction with a zone of condensation of collagen which suggests considerable pressure. The new granulation-tissue contains numerous wandering cells, of which macrophages with vesicular protoplasm form a considerable number. Immediately inside this reactive zone is a band of necrosis containing macrophages and degenerated leucocytes separated from the main central coagulum by a considerable zone of leucocytes, many of them in various stages of degeneration. Macrophages are especially numerous at the margin of the outer coagulated area. In these lesions the bacilli are obviously much increased in number. They can be seen in the outer necrotic zone, usually phagocytosed by macrophages, and in the intermediate leucocytic zone, but they are especially numerous in the central coagulum when they are diffusely scattered in single elements and larger closely intertwined groups.

Seven days: Here the lesion is much smaller, and, in passing, it may be pointed out that the local silica lesion shows invariably this rapid diminution in size, apparently dependent upon loss of fluid immediately after the cessation of the process of progressive tissue destruction. Essentially, however, the lesion is simply a later stages of the previous ones. There is still a central mass of necrotic coagulum, though it is obscured to some extent by leucocytes, and a peripheral necrotic zone with a limiting border of granulation-tissue. The number of mononuclear phagocytes has enormously increased and a considerable proportion of them contain bacilli. The appearances suggest that the bacilli which have been proliferating in the abscess are all engulfed by phagocytes, many of which wander out into the granulation-tissue at the margin of the lesion.

The experiments in which large doses of tubercle bacilli were used in conjunction with silica do not bring out quite so clearly the essential difference between the tubercle silica lesion and the tubercle lesion without silica, inasmuch as such a large number of bacilli is present in both series of lesions. Nevertheless, it is possible to appreciate the development of the bacilli in the necrotic tissue with the formation of large colonies.

CONCLUSIONS.

The conclusion we draw from these experiments is briefly as follows: The mouse possesses a high degree of natural immunity to tubercle, and even massive doses of bacilli injected beneath the skin can be tolerated fairly well. In course of time the organisms are encapsuled, and though a certain number of them escape this fate, being conveyed to distant parts by the action of phagocytes, the resulting lesion develops very slowly. With smaller doses of bacilli this tolerance is even more obvious. The isolated bacilli are phagocytosed by leucocytes and also by polyblasts, and in the latter elements they live practically symbiotically, proliferating freely within the cell, which shows no obvious evidence of damage from their presence. When silica is introduced along with the bacilli into the subcutaneous tissues of the mouse there is a very different result. The tissues undergo a considerable degree of necrosis, and though an intense leucocytosis is an important part of the accompanying reaction, the centre of the lesion remains acellular for several days and consists of a structureless coagulum. After a preliminary lag of two or three days the bacilli proliferate abundantly in this coagulum, protected from the cellular defences of the body. This protection is, however, only temporary, and in a few more days the coagulum is absorbed, and the lesion becomes infiltrated with mononuclear and polynuclear phagocytes, which absorb the bacilli with avidity. In the meantime, however, a small dose of bacilli becomes a dose of considerable magnitude, and, inasmuch as an important factor in determining an infectious process is the number of organisms introduced, a simple explanation is forthcoming of the effect of silica upon such tuberculous lesions as we have described. It is too much, of course, to claim that an exactly similar process takes place in miners' phthisis, but the presence of a definite cell poison must obviously diminish the power of the tissue reaction and so favour the progressive multiplication of the infecting bacilli.

A study of subcutaneous lesions, such as we have described, suggests that the poison does not remain in particulate form at the site of inoculation for any considerable time, but is either fixed locally or is gradually removed by phagocytes and in the tissue fluids. When present it behaves as an active cell poison, but with its gradual disappearance the normal processes of repair become evident; the necrotic tissue is replaced by organising fibrous tissue, and, finally, nothing remains but a dense scar. In the silicotic lung this scarring is the prominent feature, and though tuberculosis and silicosis may co-exist in the same organ, the characteristic fibrosis is often enough the only evidence of previous exposure to silica. It is true that in the midst of the old fibrosed nodules it is possible to distinguish particles of silica, but they are so well encapsuled that it is doubtful whether they can exert any influence on the tissues, since they can scarcely pass into solution. The question therefore arises why, in the absence of tissue necrosis, or with only a minimal amount of cell destruction, the fibrotic lungs are peculiarly liable to tuberculosis? Is the scar-tissue actually less resistant and therefore more vulnerable than normal tissues, or does the successful invasion of the tubercle bacillus depend upon the disorganisation of the circulation of the tissue fluids brought about by lymphatic obstruction?

We have attempted to investigate this point experimentally, but so far our results are not conclusive, and work is still proceeding in this direction. We have found that if subcutaneous injections of small doses of silica are made into the flank of mice at weekly intervals for several weeks an extensive fibrosis is produced. If, now, tubercle bacilli are inoculated into this altered tissue, much more considerable lesions result than in normal control mice. In our experiments these results may have been due to the fact that healing was not complete—that enough necrotic or devitalised tissue was still present to serve as a nidus for the development of the bacilli. But we have found that much the same results, both in regard to fibrosis and in the subsequent reaction to tubercle bacilli, follow the repeated injections of a suspension of carbon. Carbon injected into the subcutaneous tissues of mice remains for the most part *in sitû*. It is phagocytosed, but the phagocytes pass away to the neighbouring lymph-nodes only very slowly, and massive doses of carbon give rise, therefore, to blockage of lymphatic vessels and mechanical fibrosis. But though the end-results are similar, the mechanism of the production of the fibrous tissue in the two cases is, of course, entirely different. The silica

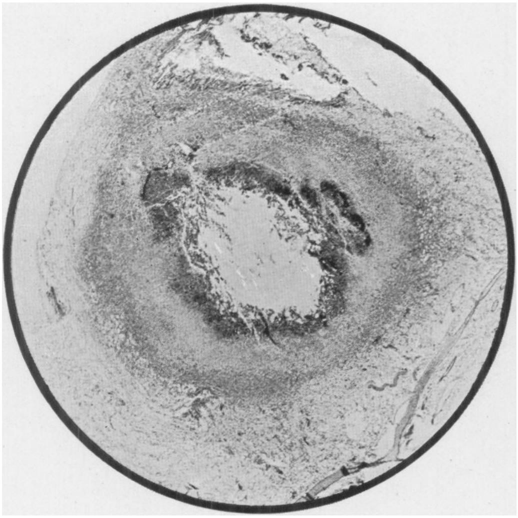

Fig. 1.—Subcutaneous lesion produced in 6 days by inoculation of 2 mgrm. of silica.

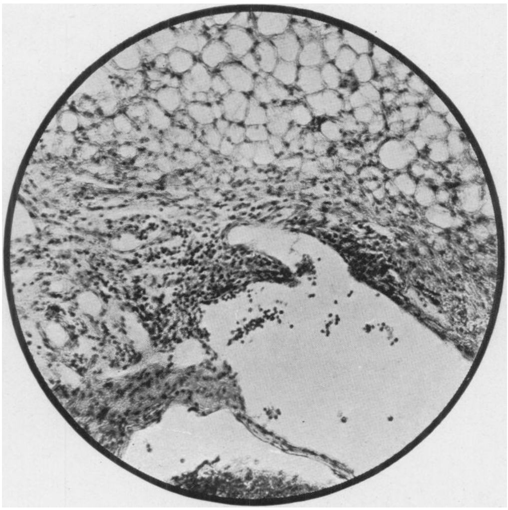

Fig. 2.—Subcutaneous lesion (7 days) following injection of fine emulsion of tubercle bacilli.

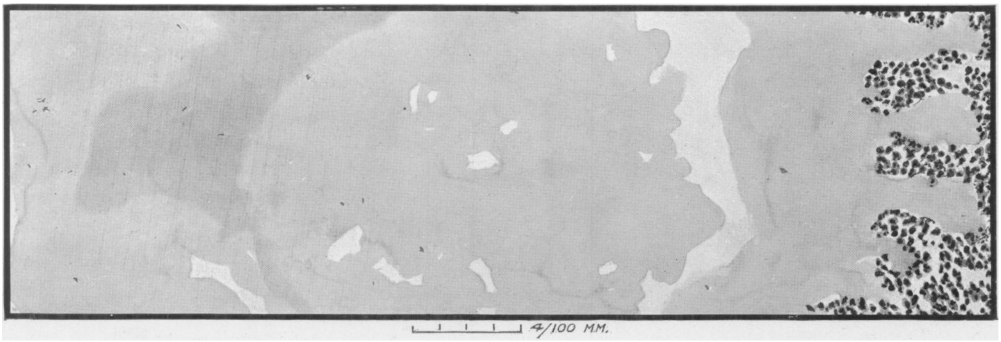

Fig. 3.—Margin of central coagulum in 3 days' silica and tubercle lesion. Early proliferation of bacilli.

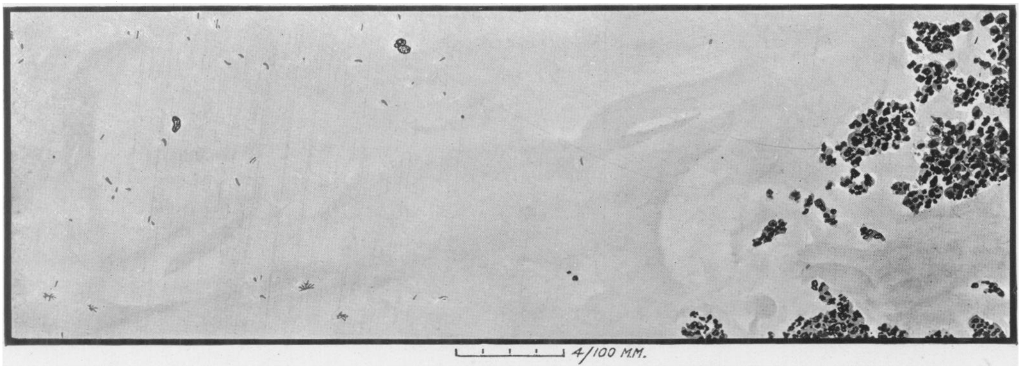

Fig. 4.—Similar lesion, but after 6 days, showing active proliferation of bacilli.

fibrosis is an end-result of a tissue destruction which cannot be produced by carbon.

It is established, of course, that coal miners are no more liable to pulmonary tuberculosis than other members of the general population, and, in point of fact, these results cannot be directly applied to the pulmonary lesions. The experimental conditions are too crude; the sudden injection of considerable localised doses of foreign substances into the tissues at irregular intervals can hardly be compared with the gradual and more or less continuous inhalation of the same substances into the lungs. Moreover, whereas the pulmonary phagocytes can deal adequately with the inert particles of carbon which reach the alveoli of the lungs, the same scavenging mechanism is not available in the subcutaneous tissues. There the carbon tends to remain within the phagocytes which have engulfed it. The phagocytes are anchored locally in considerable numbers, and must eventually die and disintegrate, and in this way sufficient pabulum may be produced to provide favourable conditions for the growth of the bacilli. Further investigations, it is hoped, may throw more light on this aspect of the problem, but at present we are unable to offer any satisfactory solution.

[The photographs from which figs. 1 and 2 have been made were taken by our colleague, Mr. J. E. Barnard, to whom we express our thanks.]

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